

Please amend the application as follows:

In the Claims

Please cancel Claims 31, 34-42, 44, 46, 47, 49-51, 55, and 59-68.

Please amend Claims 26, 28, 29, 32, 33, 48, 52, 58 and 70. Amendments to the claims are indicated in the attached "Marked Up Version of Amendments" (pages i - ii).

B<sup>1</sup> 26. (Amended) A cellular-based cardiac biological pacemaker comprising at least one cell transfected or transduced with at least one ~~gene~~<sup>C</sup> that upregulates heart rate or alters cardiac rhythm suitable for localized ~~gene~~ expression in mammalian cardiac atrial tissue.

28. (Amended) The cardiac pacemaker of Claim 26 wherein the gene is selected from the group consisting of: a  $\beta_2$ AR gene,  ~~$\beta_1$ AR gene~~<sup>C</sup>, and  $G_{as}$  gene.

B<sup>2</sup>  
Sub C2 29. (Amended) The cardiac pacemaker of Claim 28 wherein gene expression is regulated by at least one expression control element

C<sup>3</sup> 32. (Amended) The cardiac pacemaker of Claim 30 further wherein the cell is isogenic, allogenic, or xenogenic.

B<sup>3</sup> 33. (Amended) A method of regulating cardiac pacemaking activity in a mammal by introducing a biologic pacemaker according to Claim 26 into the sinoatrial node region of a mammalian heart.

B<sup>4</sup> 48. (Amended) A method of ~~regulating~~<sup>C</sup> cardiac pacemaking activity in a mammal by introducing a biological pacemaker according to Claim 45 into an atrial chamber of a mammalian heart.

- BC6
52. (Amended) The method of Claim 33 wherein the biological pacemaker is a cellular-based cardiac pacemaker construct comprising a transfected or transduced cell expressing a  $\beta$ 2-adrenergic receptor and further wherein the method comprises *in vivo* administration of an adrenergic agonist.

- B6
58. (Amended) A method of regulating cardiac pacemaking activity in a mammal by introducing a biologic pacemaker according to Claim 56 into the sinoatrial node region of a mammalian heart.

- B7C8
70. (Amended) A method of regulating cardiac pacemaking activity in a mammal by introducing a molecularly-mediated cardiac pacemaker construct comprising at least one gene that upregulates heart rate or alters cardiac rhythm suitable for localized stable gene expression in mammalian cardiac atrial tissue, wherein said construct is introduced by direct myocardial injection or endocardiac transfection or transduction.

Please add new Claims 72-77.

- sub C9
72. The method of Claim 70, wherein the cardiac pacemaker construct is introduced into the sinoatrial node region of a mammalian heart.

- B8
73. The method of Claim 70, wherein the biological pacemaker is a molecular-mediated cardiac pacemaker construct comprising a gene encoding a  $\beta$ 2-adrenergic receptor, and further wherein the method comprises *in vivo* administration of an adrenergic agonist.

74. The method of Claim 73, wherein the adrenergic agonist is isoproterenol.

75. The method of Claim 70, wherein the gene is selected from the group consisting of: a  $\beta_2$ AR gene,  $\beta_1$ AR gene, and  $G_{as}$  gene.

B 8

Sub  
C10

76. A cell transduced or transfected with at least one gene that increases the rate of contraction of the cell.

77. The cell of Claim 76, wherein the gene is selected from the group consisting of: a  $\beta_2$ AR gene,  $\beta_1$ AR gene, and  $G_{as}$  gene.

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#### REMARKS

Claims 31, 34-42, 44, 46, 47, 49-51, 55, and 59-68. have been canceled. Claims 26, 28, 29, 32, 33, 48, 52, 58 and 70 have been amended, and Claims 72-77 have been added to further and more particularly define that which Applicants regard as their invention.

Support for these amendments to the claims is found throughout the specification. Delivery of molecularly engineered cells is described, for example, on page 9, lines 25 through page 10, line 2; and page 13, lines 9-23; page 15, lines 7-21; page 16 lines 5-22. Delivery of constructs by direct DNA injection is described, for example, on page 12, line 26 through page 13, line 3; and Example 3. The term "pacemaker" is described, for example, on page 11, line 17 through page 12, line 18. Expression control elements are described, for example, on page 12, lines 2-11.

#### Objection to Claims 33, 34, 46 and 47

The Examiner objects to Claims 33, 34, 46 and 47 as containing informalities. Applicants have canceled Claims 34, 46 and 47, and amended Claim 33 as suggested by the Examiner, thereby obviating the objections. Withdrawal of the objections is respectfully requested.